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| EXAMINER | |
|---|---|
| SULLIVAN, DANIEL M | |

| ART UNIT | PAPER NUMBER |
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| 1636 | 12 |

DATE MAILED: 12/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/802,518 | Applicant(s) VAN NEST, GARY | |
|---|---|---|---|
| | Examin r Daniel M Sullivan | Art Unit 1636 | |

*-- The MAILING DATE of this communication app ars on the cover sheet with th correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

This Non-Final Office Action is a reply to the "Response Under 37 C.F.R. §1.111" filed October 9, 2002 (Paper No. 10) in response to the First Office Action on the Merits mailed April 10, 2002 (Paper No. 7). Claims 1-35 are pending and under consideration in the application.

### *Drawings*

The drawings were objected to in Paper No. 7 for reasons set forth in the PTO-948 attached thereto. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

### INFORMATION ON HOW TO EFFECT DRAWING CHANGES

**1. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

**2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.**

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to

be made, other than correction of informalities, unless the examiner has approved the proposed changes.

**Timing of Corrections**

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

***Response to Arguments***

Rejection of claims 1-9 and 29-35 under 35 U.S.C. § 112, first paragraph, as lacking enablement is withdrawn. In response to the rejection, Applicant points out that teachings set forth in the specification demonstrate that application of an immunostimulatory sequence immediately after exposure to herpes simplex virus significantly reduces the number of mice that become symptomatic. Applicant further points out that the literature cited by the examiner as evidence for unpredictability in the art is directed to problems encountered in obtaining therapeutic expression from a nucleic acid using present gene transfer techniques. As the mechanisms involved in the immunostimulatory action of DNA molecules comprising 5'-CpG-3' sequences clearly does not require expression of a gene encoded by the DNA molecule (see Agarwal and Kandimalla (cited as Ref. No. 13 in Paper No. 11) page 114, column 2, first and second paragraphs), the cited art does not speak to the predictability of the instant methods.

Rejection of claims 10-19 and 20-28 under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims is withdrawn. As above, the art relied upon by the examiner to establish the unpredictability in the art is directed to therapies that require expression

from a transferred DNA molecule for therapeutic effect. For the reasons cited above, the art does not apply to the instant invention.

Rejection of claims 29-35 under 35 U.S.C. § 112, second paragraph, is withdrawn in view of the clarification provided (Paper No. 10, page 10).

Claims 29-32 and 35 stand rejected under 35 U.S.C. § 102(a) and 102(e) as being anticipated by Krieg *et al.* (1999, *Journal of Gene Medicine*, vol. 1, pp. 56-63) and Krieg *et al.* (U.S. Patent No. 6,218,371), respectively (hereinafter referred to in combination as Krieg *et al.*). In response to the rejection, Applicant argues that Krieg *et al.* "does not disclose a composition comprising an ISS-containing polynucleotide nor a kit that does not comprise a herpes simplex virus antigen...does not disclose the claimed element of instructions for administration of the composition to an individual infected with, exposed to or at risk of being exposed to herpes simplex virus...does not mention herpes virus".

Applicant's arguments have been fully considered but they are not persuasive. Claim 12 of Krieg *et al.* (U.S. Patent No. 6,218,371), is directed to a composition comprising an ISS-containing polynucleotide. The claimed composition comprises all of the patentable limitations of claims 29-32 and 35. As pointed out in the previous Office Action, Krieg *et al.* (1999, *Journal of Gene Medicine*, vol. 1, pp. 56-63) teaches immunostimulatory sequences that meet the limitations of claims 29-32 and 35.

Although Krieg *et al.* does not teach that the composition should be used to treat herpes virus, there is no evidence that the composition of Krieg *et al.* could not be used for that purpose.

Furthermore, the intended use for the composition appears in the preamble of claim 29. Applicant is reminded that, "[i]f the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also Rowe v. Dror, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997)" (M.P.E.P. 2111.02).

With regard to instructions, the examiners assertion on page 10 of the Office action that, "mere printed matter cannot impart a patentable feature on a claim" and citation of *In re Gulack* 217 USPQ 401 (1983) are proper. Applicant asserts that the decision in *In re Gulack* provides that the inclusion of instructions for use as a component of a composition should be afforded patentable weight, particularly pointing out that, "[d]ifferences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of printed matter" and "the board cannot dissect a claim, excise the printed matter from it, and declare the remaining portion of the mutilated claim to be unpatentable..". While it is true that the Court held that printed matter *can* carry patentable weight, the Court states that "[w]here the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the art in terms of patentability" (first full paragraph on page 404). Applicant argues that the instructions for administering the composition are functionally related to the composition comprising an ISS to be administered but does not provide an explanation of how function of the composition is altered by the presence of instructions. There is no reason to

believe that the composition taught by Krieg *et al.* would not be functional in the treatment of herpes virus infection simply because it was not packaged with instructions. Therefore the composition taught by Krieg *et al.* anticipates all of the patentable limitations of the instant claims.

***New Rejections***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing symptoms of, reducing severity of or reducing recurrence of a symptom of herpes infection in mice and guinea pigs challenged with herpes virus, by administering the *phosphorothioate* polynucleotide comprising the immunostimulatory sequences set forth as SEQ ID NO:1 and 9 to said mice and guinea pigs at a dose sufficient to prevent, or reduce severity or recurrence of a symptom of herpes infection, does not reasonably provide enablement for a method of reducing the severity of a symptom of herpes virus infection in any individual or mammal comprising administering any sequence comprising 5'-C,G-3' sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

*The nature of the invention*: The claims are drawn to methods and compositions to be used in the treatment of herpes virus infection, said methods and compositions comprising ISS sequences.

*The breadth of the claims*: Given their broadest reasonable interpretation, the claims encompass methods and compositions for treatment of herpes virus infection in all individuals and mammals using any nucleic acid sequence comprising the dinucleotide sequence 5'-C,G-3'.

*The state of the prior art and level of predictability in art*: The use of CpG sequences as an immunostimulatory adjuvant is well know in the art. However, according to the teachings of Agarwal and Kandimalla (*supra*), published well after the effective filing date of the instant application, "Although the presence of an unmethylated CpG dinucleotide is essential for the induction of an immunostimulatory activity, the sequences flanking the CpG dinucleotide also play a role", human immune cells respond poorly to the hexameric motif found to be optimal in activating the mouse immune system "suggesting that the sequences required for CpG-related immune stimulation varies from species to species" and "the optimal CpG sequence requirement

for many other animal species is not known" (beginning page 114, column 2 final paragraph and continued through the first paragraph of page 115). These comments demonstrate the high degree of uncertainty in the art with regard to extending results obtained using ISS DNAs in one species to other species of mammals. In particular, Hartmann *et al.* (2000) *J. Immunol.* 164:1617-1624 teach that findings obtained using ISS in mice could not be extended to humans. Hartmann *et al.* teach, "[r]ecently, we found that phosphorothioate ODN with the purine-purine-CG-pyrimidine-pyrimidine formula that had been identified as the most stimulatory motif in mice show no or only weak activity in human immune cells" (final paragraph on page 1617) and conversely, "[t]he human stimulatory ODN...shows weaker activity in mice compared with the highly active murine CpG ODN...supporting the concept of species specificity of CpG DNA recognition by immune cells" (second paragraph on page 1622). Hartmann *et al.* also teach that the effectiveness of any given ISS is unpredictable even within closely related mammalian species. In the second paragraph on page 1622, Hartmann *et al.* teach, "[a]lthough ODN 2006 was active in vitro in all primates tested, other CpG ODN, such as ODN 2007, had relatively high activity in human immune cells but no or a weaker effect in chimpanzees and rhesus monkeys." These teachings demonstrate that the skilled artisan would not be able to use the oligonucleotide sequences or teachings set forth in the specification, which disclose methods and compositions for treating herpes virus infections in mice and guinea pigs, to treat herpes virus infection in other mammals, and humans in particular. With regard to the effectiveness of CpG oligonucleotides in stimulating immune responses in individuals outside of the genus *mammalia*, the variability even within mammalian species provides a high degree of uncertainty in extending results obtained with mammals to other genera.

Finally, Hartmann *et al.* teaches that use of phosphorothioate backbone, or some other means of protecting the ISS from nuclease degradation is required for *in vivo* clinical utility (first full paragraph on page 1618). Thus, the teachings of the prior art indicate that only the phosphorothioate oligonucleotides taught in the present disclosure would be useful in the methods of the present invention.

*The amount of direction provided by the inventor and the existence of working examples*: The instant disclosure provides various nucleic acid sequences comprising 5'-CpG-3' and reduction to practice of phosphorothioate oligonucleotides comprising two of those sequences for the treatment of herpes virus infection in mice and guinea pigs. The disclosure does not, however, set forth teachings regarding the requirements unique to the use of CpG oligonucleotides in mammalian species outside of mice and guinea pigs.

*Relative skill of those in the art*: The level of skill in the relevant art is very high. However, because the structural determinants dictating the function of CpG sequences in individual mammalian species are unknown, the prior art does not enable the skilled artisan to extend the explicit teachings found there without significant empirical experimentation.

*The amount of experimentation required to practice the invention*: Agarwal and Kandimalla (*supra*) teach, "Studies on the medicinal chemistry of CpG DNA have just begun..." and "There is a species-dependent selectivity of CpG DNA, and the optimal CpG DNA sequences for many vertebrate species are not known yet. Medicinal chemistry could help to resolve the issues of species-selective bias of CpG DNA motifs and permit the application of CpG DNA therapeutics for treating veterinary diseases without requiring the identification of optimal sequences for each species" (page 119, column 2, first and second paragraphs of the

Concluding Remarks). These remarks show that practicing the claimed invention commensurate with its full scope would require the skilled artisan to identify, through empirical experimentation, an oligonucleotide sequence that can effectively stimulate the immune system of any and all individuals or identify the structural determinants that dictate the species specificity of CpG immunomodulation. This amount of experimentation would place an undue burden on one seeking to practice the invention commensurate with the full scope of the claims.

Thus, due to the art recognized unpredictability of obtaining stimulation of immune responses using CpG oligonucleotides and the lack of guidance in the specification or prior art with regard to how to use the invention in all individuals, it would require undue experimentation to practice the invention commensurate with the full scope of the claims.

Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method and compositions for reducing severity of a symptom of herpes virus infection in mice and guinea pigs wherein the administration is at the site of a herpes virus lesion or inoculation, is not enabling for a method and compositions wherein the composition is administered outside of the affected area.

The nature of the invention and the relative skill of those in the art are described above.

*The breadth of the claims*: The claims encompass a method of preventing or reducing severity or recurrence of a symptom of herpes virus infection wherein a composition comprising a CpG oligonucleotide is administered to an individual who has been exposed to herpes virus at any time point after exposure, and wherein the composition is administered to the individual at any site and by any route.

*The state of the prior art and level of predictability in the art*: As described above, the relevant art is at an early stage of development and many of the factors dictating the effectiveness of immunostimulation obtained with CpG oligonucleotides remain to be established. With regard to the effectiveness of systemic administration of CpG oligonucleotides and their administration without antigen, the prior art teaches that the effectiveness of immunostimulation with CpG oligonucleotides is dependent on the proximity of the antigen to the site of administration of the oligonucleotide. Weiner et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94:10833 teach that, "Injection of CpG [oligonucleotide] and antigen on the same flank was required for maximal adjuvant effect. Thus, CpG [oligonucleotide] exerts much of its adjuvant effect locally. This finding is consistent with or prior observations that footpad injection with CpG [oligonucleotide] enhances NK activity of cells in the ipsilateral but not contralateral lymph node" (see page 10834, column 1, final paragraph through the first paragraph of column 2 and Figure 4 and the caption thereto). This teaching introduces uncertainty as to whether "an amount sufficient to prevent a symptom of herpes virus infection" could be achieved in embodiments of the instant invention wherein the CpG oligonucleotide is administered away from the site of antigen. Because the claimed invention is drawn to administration of the CpG oligonucleotide without antigen, antigen is provided by the active infection at the site of the lesion and therefore the teachings of the prior art introduce uncertainty as to whether the invention would be operable when CpG oligonucleotides are administered away from the lesion. Based on the teachings of the prior art the skilled artisan would not predict that embodiments of the claimed invention wherein the CpG oligonucleotide is administered away from antigen provided by the active infection would be operable.

*The amount of direction provided by the inventor and the existence of working examples*: As described above, the prior art provides no working examples of those embodiments of the invention wherein the CpG oligonucleotide is administered away from a source of antigen. The teachings of the prior art suggest that the effectiveness of administration away from the site of antigen is, at best, unpredictable. The specification only describes, in specific terms, embodiments of the invention wherein the CpG oligonucleotides are administered topically at the site of inoculation with herpes virus (see especially Examples 1 and 2). These teachings do not provide the skilled artisan with the guidance required to practice the invention commensurate with the full scope of the claims.

*The amount of experimentation required to practice the invention*: Practicing the full scope of the claimed invention would require the skilled artisan to devise a means to prevent, delay development or reduce the severity of a symptom of herpes virus infection by administering a CpG oligonucleotide, without co-administration of an antigen, at sites other than those directly affected by herpes virus. The teachings of both the prior art indicate that there are barriers to accomplishing this, but neither the prior art nor the specification provides guidance as to how these barriers can be overcome. The skilled artisan would therefore have to engage in empirical experimentation to develop a means to administer an amount of CpG oligonucleotide at locations away from the site of active herpes virus infection.

Thus, due to the uncertainty provided by the teachings of the prior art with regard to delaying development of a symptom of herpes virus infection by administration of a CpG oligonucleotide, without co-administration of an antigen, away from the site of herpes virus exposure, and the absence of teachings with regard to how to overcome the barriers to achieving

effective immunostimulation in the absence of antigen, practicing the claimed invention commensurate with its full scope would place an undue burden of empirical experimentation on the skilled artisan.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
December 16, 2002

JAMES KETTER
PRIMARY EXAMINER